REMARKS

Status of the Claims

Claims 1-3 and 11-12 stand rejected. Claims 2 and 11-12 have been canceled without prejudice or disclaimer. Applicants expressly reserve the right to file divisional and/or continuation applications or take such other appropriate measures deemed necessary to protect the subject matter of the canceled claims.

Claim 1 has been amended to incorporate the subject matter of claim 11. Support for this amendment can be found, for example, in original claim 11. Claim 1 has also been amended to recite a total concentration of cholesterol and cholesterol ester is greater than 0.08 mg/ml of a culture medium. Support for this amendment can be found, for example, on page 7, lines 7-9, in the specification.

New claims 15 and 16 have been added. New independent claim 15 is drawn to a method of proliferating eukaryotic cells and encompasses the subject matter of originally pending generic claim 1. Original claim 1 was the generic claim to the species that was elected during supplemental restriction. Support for new claim 15 can be found, for example, in original claim 1, and in the specification at page 6, line 18, page 4, lines1-5, and page 7, lines 7-9. New claim 16 is dependent on claim 15 and recites the sLDL particles comprise a peptide and that these sLDL particles comprising a peptide increase eukaryotic cell proliferation by at least 50% relative to cells cultured in the absence of the sLDL particles comprising a peptide and in the presence of foetal calf serum or other serum free lipid supplements. Support for this amendment can be found, for example, in the specification at page 4, line 26 continuing through to page 5, line 2, and page 6, line 18.

New claim 17 has been added and is drawn to a method of making sLDL particles. Support for new claim 17 resides, for example, in the specification at page 21, lines 7-17, page 8, lines 1-2, and page 8, line 23 continuing through line 7 on page 9.

No new matter has been added by way of these claim amendments.

Claims 1, 3 and 15-17 are pending.

Reexamination and reconsideration of the application as amended are respectfully requested in view of the following remarks.

The Rejection of the Claims Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1-3 and 11-12 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Baillie *et al.* (J of Lipid Research, Vol. 43, No.1 January 2002, page 69-73) in view of Mainwaring and Wayte (U.S. Patent No. 7,258,998) and further in view of Gorfien *et al.* (Biotechnology Progress, September 2000, Vol. 16, No. 5, pages 682-687).

Applicants respectfully note that a *prima facie* case of obviousness under 35 U.S.C. § 103(a) requires that a combination of references places the claimed subject matter in the public domain prior to Applicants' date of invention. See *In re Zenitz*, 333 F.2d 924, 142 USPQ 158 (C.C.P.A. 1964). Thus, establishing a *prima facie* case of obviousness requires that the cited references can be combined such that each and every element of the claimed invention is taught, explicitly or implicitly, by the references, and that a reasonable expectation of success exists in such a combination. As the Supreme Court has clarified, obviousness under § 103 still requires consideration of the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including an analysis of the scope and content of the prior art and the difference between the claimed subject matter and the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 14 (2007).

Baillie *et al.* teach a cholesterol concentration of 80 μmol/l or 0.03 mg/ml, and this is acknowledged by the Examiner in the previous Office Action mailed November 23, 2010 (see bottom of page 4 and top of page 5) and again in the current Office Action mailed July 6, 2011 (see bottom of page 4 through line 1 of page 5). As noted above, Applicant has amended claim 1 to recite that the total concentration of cholesterol and cholesterol ester is greater than 0.08 mg/ml, which is over *double* that taught in Baillie *et al.*

Applicant submits that the claims as amended are not obvious in view of the cited references. Firstly, based on the teaching of Baillie *et al.*, one of skill in the art would in fact view the use of sLDL particles as not being a useful alternative to FCS and there would be no suggestion that increasing the amount of cholesterol or cholesterol ester would in fact improve the situation. Moreover, the method of preparing the sLDL particles as taught by Baillie *et al.* is a multi-stage process which includes centrifugation and extrusion. An important difference is

that the present invention teaches a method of making sLDL particles which involves a one stage microfluidisation process which allows much *higher* concentrations of cholesterol/cholesterol ester to be employed in the sLDL particles. Baillie *et al.*, however, is limited by the methodology of the time period. The method used by Baillie *et al.* for preparing the sLDL particles was by lyophilisation, followed by reconstitution, followed by sonication and then extrusion, which results in limited volume and concentration of sLDL particles.

The instant claims, however, recognize the importance of cholesterol/cholesterol ester and teach that up to 0.5-1 mg/ml may be employed (see page 7, second paragraph). Cholesterol is one of the main neutral lipid components of mammalian biological membranes making up about 20-50% of the membrane mass, depending on the membrane. If a cell is to grow and divide it must make new membrane, which requires cholesterol either from an extra-cellular or intra-cellular source. In media without an external source of cholesterol, the cell must synthesize cholesterol, which takes time and energy. If an extra-cellular source of cholesterol is available in the media, the cell can simply use that, which saves time and energy for the cell and, as supported by the present invention, allows for faster proliferation. However, cholesterol has particularly poor water solubility (0.00007 mmol/l) and hence something is required to assist solubility in media. The presently claimed sLDL particles are able to achieve this solubility. It should also be appreciated that in Baillie *et al.* the cholesterol values were intended to be similar to the amount of cholesterol employed using serum supplementation and as such there was no suggestion or teaching to increase the cholesterol amounts further.

Table 4 of the present specification, describes sLDL particles with cholesterol values at an average of 2.5 mg/ml, but up to 8.8 mg/ml was achieved (note 2.5 mg/ml is equivalent to 6.5 mmol/l). As can be seen in the results in Figure 4 of the instant application, the sLDL particles can support the proliferation of cells at a level of up to 2500% of that produced using FCS supplementation alone. In this regard, it appears the Examiner is misinterpreting the teaching of Baillie *et al.* with regards to supporting cell proliferation (see page 4, second paragraph). As can be seen in Figure 2 of Baillie *et al.*, the sLDL particles of Baillie *et al.* *do not* support growth as well as FCS and in fact cells grown in media supplemented with the sLDL particles, as opposed to FCS, proliferate at much lower values. Instant claims 2 and 3, as previously presented, claim

at least a 20% and 50% increase in cell numbers *relative* to the use of FCS alone and *not* simply to an increase in cell numbers from their starting point as is presented in Baillie *et al.* In fact, the sLDL particles of Baillie *et al.* were significantly poorer at supporting cell growth as compared to FCS. Therefore, there is simply no expectation based on Baillie *et al.* that one could in fact get an increased degree of proliferation in comparison to the use of FCS, as is demonstrated by the instantly claimed sLDL particles.

Given the above claim amendments and arguments, it would not have been obvious to one of ordinary skill at the time of the invention, to look to the teachings of Baillie *et al.* to arrive at the claimed invention with any reasonable expectation of success. As none of the other cited references teach the method as claimed instantly, one of ordinary skill would not have been motivated to use Baillie *et al.*, Mainwaring *et al.* and Gorfien *et al.* alone or in combination to achieve the method of the instant claims.

As these cited references do not render obvious the presently claimed methods, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSIONS

In view of the amendments and remarks, Applicant submits that the rejections of the claims are overcome. Applicant respectfully submits that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefor (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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